

### REMARKS

Claims 1-61 are pending. Minor amendments are made and new claims 58-61 are added.

Claim 1 is amended to delete the term "isolated". In the context of a claim to a recombinant virus that is attenuated, this term is superfluous.

Amendments to claims 6, 25 and 55 are editorial in nature and merely clarify the language of these claims without altering their scope.

New claims 58-61 are supported by the specification at e.g. pp. 79-80 and by data in, e.g. Fig. 22B.

### Restriction

The Examiner has maintained the restriction requirement as originally presented. Applicants again state that, in view of linking claim 1, they are entitled to examination of claims directed to a significant number of species upon finding of allowance of the generic linking claim. At least all of claims 1-27, which are directed to species in which expression of one or more HMPV genes is somehow ablated, should be examined upon allowability of claim 1.

Applicants reserve the right to petition the restriction requirement should the Examiner persist in failing to examine a reasonable number of species of the invention upon a finding that the elected species (ablation of M2-2 protein expression) is allowable over the prior art.

Applicants further request that the Examiner acknowledge rejoinder for consideration of methods of use of the elected composition of matter claims upon a finding that such compositions are allowable.

### Double patenting

The Examiner objects to claim 8 as being substantially a duplicate of claim 18. This is a result of the Examiner improperly restricting the scope of examination, not due to distinction in claim scope. Applicants decline at this time to cancel either claim pending the completion of examination.

Rejection under 35 USC § 112, second paragraph

Claims 6, 25, 55 and 56 are rejected under 35 USC § 112, second paragraph, as allegedly being vague and indefinite. The particular reasons for rejection are set forth on p. 4 of the Office Action.

Applicants submit that the amendments to claims 6, 25, 55 and 56 above are sufficient to obviate this ground of rejection.

Rejection under 35 USC § 112, first paragraph

Claims 1-8, 15-19, 25, 26, 55 and 56 are rejected under 35 USC § 112, first paragraph, for alleged failure to comply with the written description requirement of the statute. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Examiner argues that the claims unacceptably encompass a genus of HMPV recombinants that are not sufficiently defined, based upon only the description in the specification of two species of HMPV. The Examiner asserts that the genus is highly variable and a significant number of structural variants are permitted. However, the claimed invention relates to a finding that ablation of expression of particular genes of HMPV produces a controllable level of attenuation such that these modifications of HMPV are useful in creating vaccine strains. The generic invention relates to these modifications, and their use among various HMPV, not to the other variation in HMPV itself.

The Examiner is reminded that the specification must describe only the claimed invention, not that which is not claimed.

As explained above, the feature which distinguishes the claimed invention from the known HMPV is that the genome or antigenome carries one or more mutations that ablate expression of M2-2 (the elected species) or other genes of HMPV, resulting in attenuation of growth of the virus. All of the Examiner's reasoning about potential variation in protein structure, etc. (see, e.g. p. 6 of the Office Action), is irrelevant to the present claims, since the protein in question is not expressed.

The specification, for example by the Figure 7 showing the structure of a recombinant DNA plasmid useful for recovery of virus of the invention, and the experimental examples that generated the data illustrated in Figures 8-25 of the application, make it quite clear that the Applicants were in "possession of the invention ... as now claimed" as of the filing date of the application." The instant rejection is unsustainable and must be withdrawn.

Claims 1-8, 15-19, 25, 26, 55 and 56 are rejected under 35 USC § 112, first paragraph, for alleged failure to comply with the enablement requirement of the statute. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Here the rejection fails for at least two reasons. First, like the rejection for lack of written description above, the Examiners' arguments are totally irrelevant to the claimed invention. The claimed invention relates to ablation of expression of a protein. Thus, arguments based upon lack of description of a structure-function relationship of a protein carry no weight.

Second, the Examiner bears the burden of establishing a *prima facie* case of lack of enablement of the invention before Applicants even have to respond. A proper case of lack of enablement requires consideration of various factors as to whether or not undue experimentation is required to practice the invention. *See, In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors, the Examiner considers only unpredictability. The Examiner's assertion of lack of enablement is therefore legally insufficient.

For all of the above reasons, the instant rejection must be withdrawn.

#### Rejection under 35 USC § 103

Claims 1-4, 6-8, 15, 16, 18, 25, 55 and 56 stand rejected under 35 USC § 103(a) as being unpatentable over Bermingham (1999) in view of Van den Hoogen (2001) and Van den Hoogen (2002). This rejection is respectfully traversed, reconsideration and withdrawal thereof are requested.

First, Applicants submit that the Examiner fails to establish *prima facie* obviousness of the claimed invention. In particular, one element of *prima facie* obviousness is that there must

be a reasonable expectation of success in obtaining the invention by modification of the prior art in the manner suggested by the Examiner. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants submit that, since the art of recombinant virus production is among the biotechnology arts, a field of endeavor considered “inherently unpredictable”, it is unpredictable whether the life cycle of a first virus would be mimicked by the life cycle of a different virus. The various viruses among the negative-strand RNA viruses, of which HMPV is a member, are quite different in their requirements for replication. Therefore, whatever disclosure Bermingham provides regarding the requirements for replication in RSV, that disclosure does not establish any reasonable expectation of success that the present invention, i.e. an attenuated HMPV (claim 1), can be obtained by the same genome modifications as provide that result in RSV. Accordingly, the Examiner fails to establish *prima facie* obviousness of the present invention.

The above is supported by testimony of Dr. Peter Collins, provided to the record by the attached Declaration. (Unsigned, an executed copy will follow with a supplemental response.) Dr. Collins describes several of the difficulties encountered during the development of the invention and explains how differences in the biology of RSV vs. HMPV remove any expectation of success in merely copying the technical approach of Bermingham in the instance of HMPV.

Applicants submit that the failure of the Examiner to establish *prima facie* obviousness of the invention, taken with the testimony of Dr. Collins that one of ordinary skill in the art would have no expectation of success in directly adopting the methods of Bermingham to the problem of obtaining an attenuated HMPV, mandate withdrawal of the instant rejection.

Claims 1 and 3-5 stand rejected under 35 USC § 103(a) as being unpatentable over Bermingham and the two Van den Hoogen references, in further view of Ludin (1996). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

As explained above, the combination of Bermingham and Van den Hoogen does not establish *prima facie* obviousness of the invention, and that explanation suffices for the present rejection as well. Ludin (1996) is cited for teaching that a GFP protein can be used as a marker

for gene expression or to monitor protein function (in the sense of localization). Ludin (1996) does nothing to remedy the deficiencies of the combination of Bermingham with Van den Hoogen in failing to establish *prima facie* obviousness. That is, teachings about GFP do not inform the artisan of ordinary skill of how to adapt teachings about RSV to problems to be solved in working with HMPV. Therefore, the instant rejection must be withdrawn for the same reasons as above.

Conclusion


In view of the above remarks, it is believed that claims are allowable.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell Reg. No. 36,625 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

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